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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/519,665	HINRICHS, STEVE H	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) *5-7,15,16 and 21-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8-14 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). 9 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's election with traverse of group IV, claims 1-4, 9-14, 17-22, species antibody or a subcomponent of an antibody, and species sarcoma in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the proper search for group IV, claims 1-4, 9-14, 17-22, drawn to a method for modulating EWS/ATF1 transcriptional factor mediated gene expression, claims 23-32, drawn to a method for screening for modulators of EWS/ATF1 transcriptional factor mediated gene expression, claims 46-48, drawn to a method for modulating EWS/ATF1 transcriptional factor mediated viral replication, and claims 49-55, drawn to a method for modulating EWS/ATF1 transcriptional factor mediated gene expression, is necessarily coextensive. Indeed, group IV, claims 1-4, 9-14, 17-22, drawn to a method for modulating EWS/ATF1 transcriptional factor mediated gene expression is identical to group XXXIV, claims 49-55, drawn to a method for modulating EWS/ATF1 transcriptional factor mediated gene expression.

This is not found persuasive because of the following reasons: 1) it is noted that group XXXIV, claims 49-55, was inadvertently recited as being drawn to a method for modulating EWS/ATF1 transcriptional factor mediated gene expression. Rather, group XXXIV, claims 49-55, is drawn to a method for modulating EWS/ATF1 transcriptional factor mediated cellular proliferation, which is different from the method of group IV by method objective, method steps, and reagents used. Therefore, the search for these groups are not coextensive and it would be a serious burden for the Examiner to search these two groups together. Similarly, claims 23-32, drawn to a method for screening for

modulators of EWS/ATF1 transcriptional factor mediated gene expression, claims 46-48, drawn to a method for modulating EWS/ATF1 transcriptional factor mediated viral replication are different from the method of group IV by method objective, method steps, and reagents used. Therefore, the search for these groups are not coextensive and it would be a serious burden for the Examiner to search these two groups together.

The requirement is still deemed proper and is therefore made FINAL.

After review and reconsideration, claim 8 is rejoined with group IV

Further after review and reconsideration, group IV and groups I-III, V-VI, XIII-XXXV are further subjected to the following species restriction requirement, because in a telephonic conversation with Patrick Hagan on 08/21/03, Applicant asserts that the consensus sequences derived from the linker domains as recited on page 13 of the specification are also considered as linker domains.

It is noted that claims 1, 23-24, 33, 46, 49 are linking claims, and the present and previous restrictions of paper No:4 are subjected to the nonallowance of the linking claim(s), claims 1, 23-24, 33, 46, 49. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Election/Restrictions

Restriction to one of the following species is required under 35 U.S.C. 121:

The linker domain of the elected transcriptional factor is an amino acid domain of the transcriptional factor or a corresponding consensus sequence.

The inventions are distinct, each from each other because of the following reasons:

The species are distinct, because they have different structure.

Because these inventions are distinct for the reason given above, and further, because the searches for the groups are not co-extensive, and therefore, it would be a serious burden for the Examiner to examine all the species together, restriction for examination purposes as indicated is proper.

Applicants are required under 35 USC 121 to elect a single disclosed species

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 USC 103 of the other invention.

Applicants are reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendement of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(h).

In a telephonic conversation with Patrick Hagan on 08/21/03, Applicant elects species SEQ ID NO:1. Iis required that in the reply to this Office action, the species election is confirmed by Applicant.

Accordingly, claims 1-4, 8-14, 17-20, the transcriptional factor EWS/ATF1, its linker domain of species residues 205-219 of the ATF1 of SEQ ID NO:1, species antibody or subcomponent of an antibody and species sarcoma are examined in the instant application. Claims 21-22 are withdrawn from consideration as being drawn to non-elected species.

It is noted that due to the election of the species antibody, issues concerning the language "inhibitory agent", such as written description and enablement is delayed until

the time of allowance, if the claims are allowable, at which time all species of the inhibitory agent will be considered. Similarly, due to the election of the species "sarcoma", issues concerning the language "cancer" of claim 8, or "mesenchymal tumors" of claim 11, such as scope of enablement, is delayed until the time of allowance, if the claims are allowable, at which time all species of cancer will be considered.

OBJECTION

1. The specification is objected because the recited references to support the disclosure in the specification do not seem to match with the disclosure in the specification. For example, Hileman, 1994, Bioconjugate Chem, 5: 436-444 was cited after the disclosure that interference with DNA binding and transcriptional activity by the AFT-1-inhibitory sFv demonstrated EWS/ATF1 is important for maintenance of tumor cell viability in addition to its previously proposed role in inhibiting the neoplastic process (p.22, last line bridging p.23). However, Hileman et al, 1994, teach synthesis and characterization of conjugates formed between periodate-oxidezed ribonucleotides and amine-containing fluorophores, which is not remotely related EWS/ATF1.

2. Claims 8 and 13 are objected to for the use of the language "involved". It is not clear how the transcriptional factor is "involved" in cancer, and how a gene or a portion of a gene is "involved" in the translocation.

PRIORITY DATE

The Examiner has established a priority date, March 06, 2000 for the instantly claimed application serial number 09/519665 as the applications SN=08/881800 and 08/219880 to which priority is claimed do not recite the limitation of a method for modulating transcriptional factor-mediated gene expression, wherein the transcriptional factor is "EWS/ATF1". Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 1-4, 8-14, 17-20 are rejected under 35 USC 112, first paragraph.

Claims 1-4, 8-14, 17-20 are drawn to a method for modulating "transcriptional factor"-mediated gene expression, comprising exposing said transcriptional factor to an inhibitory agent which binds to "a linker domain of said transcriptional factor", wherein said linker domain is located adjacent to the DNA binding domain of the transcriptional factor, wherein the inhibitory agent binds with sufficient binding affinity to modulate transcription of a gene. The transcriptional factor has a DNA-binding domain distinct from an activation domain. Said modulation comprises dissociation of the transcriptional factor from the DNA of said gene and inhibits binding of the transcriptional factor to the DNA of the gene. The transcriptional factor is involved in a specific disease process,

which is sarcoma. The transcriptional factor comprises an oncogenic fusion protein with a DNA-binding function. The fusion protein is tumor specific, or specific for mesenchymal tumors. The fusion protein is encoded by a chromosomal translocation comprising two or more genes or portions of genes. Said gene or portion of gene is a b-ZIP transcription factor ATF1 and said fusion protein is EWS/ATF1. The inhibitory agent is an antibody or a subcomponent of an antibody, or a monoclonal antibody.

The specification discloses that b-Zip transcriptional factors such as ATF1, CREB and CREM, regulate transcription through binding to cyclic responsive elements (CRE), following activation of certain pathways, such as protein kinase A (PKA) (p. 21).

The specification discloses four antibodies mAb1, mAb3, mAb4 and mAb5 that bind to the transcriptional factor ATF1 (Example 5, p.53.-54). The specification discloses that antibodies mAb1 and mAb3 binds to amino terminal half of ATF1, which contains domains involved in transcriptional activation, and that antibody mAb1, but not mAb3 increases transcription of said PCNA protein. More importantly, the specification discloses that antibody mAb4 inhibits transcription using a murine proliferating cell nuclear antigen gene promoter (PCNA) as template (p.52), and that expression of sFc4 in Hela cells transfected with pEWS/ATF1 decreases the reporter CRE-luc expression, suggesting that sFv4 is capable of inhibiting CRE activation by EWS/ATF1 in Hela cells, and consequently inhibiting transcription of genes (Example 17 on pages 85-86). The specification also discloses that expression of sFv4 in tumor cell line SU-CCS-1 endogenously expressing EWS/ATF1 fusion protein decreases the expression of CRE-luc reporter, and leads to loss of viability and apoptosis (Examples 17-18, on pages 86-

90). Moreover, the specification discloses that although full length mAb4 does not inhibit CREB binding to DNA, sFv4 inhibits both ATF-1 and CREB binding to DNA (Examples 9-10 on pages 58-61).

The specification discloses that although both antibodies mAb 4 and mAb5 reacts with the carboxy-terminal half of ATF1 which includes the leucine zipper and DNA binding domain, only antibody mAb4, but not antibody mAb5, inhibits transcription (p.52). The specification also discloses that antibody mAb4 specifically binds to peptide (c) or amino acids 205-219 of ATF1 protein of SEQ ID NO:1, whereas mAb5 binds to peptide (d) or amino acids 185-205 of ATF1 protein of SEQ ID NO:1 (Examples 5-6 on pages 53-55).

The specification discloses that it has been determined that amino acids 205-219 of ATF1 protein of SEQ ID NO:1 is a linker domain for ATF1 (p.12), wherein a linker domain is a unique sequence for transcriptional factors, such as the linker domains of ATF1, CREB and GCN4 (members of the b-ZIP family), that has been determined to be the epitope of mAb41.4, and wherein the linker domain links the transcription activation domain (TAD) to the DNA binding domain and optionally dimerization region (p. 14).

The specification discloses that 37 members of the b-ZIP family have putative linker domains characterized by their uniqueness and their position between the b-ZIP-domain and the transcription activation domain (TAD) (. 14, last line bridging p.15). The specification discloses that the linker domains are present in other families of transcriptional factors, such as helix-turn helixs and zinc finger proteins (p. 15, first paragraph).

The specification discloses that the interaction of the sFv with the key domain in a transcriptional factor prevents the binding of the factor to DNA, and this embodiment of the claimed invention can be applied to any transcriptional factor (p.18).

It is noted that there is no actual published references supporting such disclosure of "putative" linker domains of 37 members of the b-ZIP family and of other families of transcriptional factors, such as helix-turn helixs and zinc finger proteins in the specification. There is no disclosure of an example of disruption of transcriptional factors, other than ATF-1 and CREB, using antibodies to a linker domain different from the two linker domains having a common epitope for sFv4 as described for ATF-1 and CREB. In other words, there is only a single example of sFv4 that can bind to both the linker domain of the transcriptional factors of the b-ZIP family ATF-1 and CREB, and disrupt the transcription of gene expression.

The claims encompass a method for modulating gene expression mediated by any transcriptional factor, or any oncogenic fusion protein with a DNA-binding domain, or fusion of any two or more genes.

The structure of different transcriptional factors and their putative linker domains are however different and are not necessarily exposed such that an antibody fragment sFv could bind to. Roitt et al, 1998, Immunology, 4th ed, Mosby, London, p. 7.7-7.8 teach that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that only a certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. These regions are often at exposed areas on the outside of the

antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (p.7.7-7.8). This is exemplified by the teaching of Holmes (Exp. Opin.Invest. Drugs, 2001, 10(3):511-519) who teaches that rabbits were immunized with synthetic peptides which in each case generated high anti-peptide specific immunoreactivities, however, none of the antibodies exhibited binding to the full length antigen. The author concludes that 'Presumably, expression of these epitopes in the context of the protein was important and affected the antibody binding ability (p. 513, col 1). Herbert et al. (The Dictionary of Immunology, Academic Press, 4th edition; 1995, p.58) define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein the 3-dimensional structure of the protein molecule may be essential for antibody binding.

The specification however has not described the genus of antibodies that could bind to and disrupt the binding of any transcriptional factor to DNA. The instant disclosure of a single species of sFv4 does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera.

Further, the specification has not described the genus of transcription factors and their linker domains, wherein binding of an antibody to the linker domains would disrupt binding of the transcription factor to DNA.

Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written

description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific sfv4 and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed. Thus, only a method for inhibiting "EWS/ATF1 transcriptional factor"-mediated gene expression, comprising exposing said transcriptional factor to the antibody fragment sFv4 which binds to the linker domain comprising amino acids 205-219 of the ATF1 protein of SEQ ID NO:1, wherein said linker domain is located adjacent to the DNA binding domain of the transcriptional factor, wherein the antibody fragment sFv4 binds with sufficient binding affinity to decrease transcription of a gene, but not the full breadth of the claims meet the written description provisions of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Claims 1-4, 8-14, 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method for inhibiting EWS/ATF1 transcriptional factor-mediated gene expression, comprising exposing said transcriptional factor to the antibody fragment sFv4 which binds to the linker domain comprising amino acids 205-219 of the ATF1 protein of SEQ ID NO:1, does not reasonably provide enablement for a method for modulating gene expression mediated by "any transcriptional factor", or "any fusion protein", comprising exposing said transcriptional factor to an inhibitory agent which binds to a linker domain of said transcriptional factor, wherein said linker domain is located adjacent to the DNA binding domain of the transcriptional factor, wherein the inhibitory agent binds with sufficient binding affinity to modulate transcription of a gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-4, 8-14, 17-20 are drawn to a method for modulating "transcriptional factor"-mediated gene expression, comprising exposing said transcriptional factor to an inhibitory agent which binds to "a linker domain of said transcriptional factor", wherein said linker domain is located adjacent to the DNA binding domain of the transcriptional factor, wherein the inhibitory agent binds with sufficient binding affinity to modulate transcription of a gene. The transcriptional factor has a DNA-binding domain distinct from an activation domain. Said modulation comprises dissociation of the transcriptional factor from the DNA of said gene and inhibits binding of the transcriptional factor to the

DNA of the gene. The transcriptional factor is involved in a specific disease process, which is sarcoma. The transcriptional factor comprises an oncogenic fusion protein with a DNA-binding function. The fusion protein is tumor specific, or specific for mesenchymal tumors. The fusion protein is encoded by a chromosomal translocation comprising two or more genes or portions of genes. Said gene or portion of gene is a b-ZIP transcription factor ATF1 and said fusion protein is EWS/ATF1. The inhibitory agent is an antibody or a subcomponent of an antibody, or a monoclonal antibody.

The disclosure of the specification has been set forth above.

Briefly, the specification discloses that antibody mAb4 inhibits transcription using a murine proliferating cell nuclear antigen gene promoter (PCNA) as template (p.52), and that expression of sFc4 in Hela cells transfected with pEWS/ATF1 decreases the reporter CRE-luc expression, suggesting that sFv4 is capable of inhibiting CRE activation by EWS/ATF1 in Hela cells, and consequently inhibiting transcription of genes (Example 17 on pages 85-86). The specification also discloses that expression of sFv4 in tumor cell line SU-CCS-1 endogenously expressing EWS/ATF1 fusion protein decreases the expression of CRE-luc reporter, and leads to loss of viability and apoptosis (Examples 17-18, on pages 86-90). Moreover, the specification discloses that although full length mAb4 does not inhibit CREB binding to DNA, sFv4 inhibits both ATF-1 and CREB binding to DNA (Examples 9-10 on pages 58-61). The specification also discloses that antibody mAb4 specifically binds to peptide (c) or amino acids 205-219 of ATF1 protein of SEQ ID NO:1.

It is noted that there is no actual published references supporting such disclosure of "putative" linker domains of 37 members of the b-ZIP family and of other families of transcriptional factors, such as helix-turn helixs and zinc finger proteins in the specification. There is no disclosure of an example of disruption of transcriptional factors, other than ATF-1 and CREB, using antibodies to a linker domain different from the two linker domains having a common epitope for sFv4 as described for ATF-1 and CREB. In other words, there is only a single example of sFv4 that can bind to both the linker domain of the transcriptional factors of the b-ZIP family ATF-1 and CREB, and disrupt the transcription of gene expression.

The claims encompass a method for modulating gene expression mediated by any transcriptional factor, or any oncogenic fusion protein with a DNA-binding domain, or fusion of any two or more genes.

The structure of different transcriptional factors and their putative linker domains are however different and are not necessarily exposed such that an antibody fragment sFv could bind to. Roitt et al, 1998, Immunology, 4th ed, Mosby, London, p. 7.7-7.8 teach that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that only a certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. These regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (p.7.7-7.8). This is exemplified by the teaching of Holmes (Exp. Opin.Invest. Drugs, 2001, 10(3):511-519) who teaches that rabbits were immunized with synthetic

peptides which in each case generated high anti-peptide specific immunoreactivities, however, none of the antibodies exhibited binding to the full length antigen. The author concludes that 'Presumably, expression of these epitopes in the context of the protein was important and affected the antibody binding ability (p. 513, col 1). Herbert et al. (The Dictionary of Immunology, Academic Press, 4th edition, 1995, p.58) define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein the 3-dimensional structure of the protein molecule may be essential for antibody binding. Thus, it is unpredictable that antibodies to a linker domain of any transcriptional factor or any fusion protein could bind to the transcriptional factor or said fusion protein, and inhibits binding of the transcriptional factor or the fusion protein to DNA. The specification however has not disclosed how to make the genus of antibodies that could bind to and disrupt the binding of any transcriptional factor to DNA.

In view of the above it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph rejection 1-4, 8-14, 17-20 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *"in vitro"* method for inhibiting EWS/ATF1 transcriptional factor-mediated gene expression, comprising exposing said transcriptional factor to the antibody fragment sFv4 which binds to the linker domain comprising amino acids 205-219 of the ATF1 protein of SEQ ID NO:1, does not reasonably provide enablement for an "in vivo" method for modulating gene expression mediated by a transcriptional factor,

comprising exposing said transcriptional factor to an inhibitory agent which binds to a linker domain of said transcriptional factor, wherein said linker domain is located adjacent to the DNA binding domain of the transcriptional factor, wherein the inhibitory agent binds with sufficient binding affinity to modulate transcription of a gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-4, 8-14, 17-20 are drawn to a method for modulating transcriptional factor-mediated gene expression, comprising exposing said transcriptional factor to an inhibitory agent which binds to "a linker domain of said transcriptional factor", wherein said linker domain is located adjacent to the DNA binding domain of the transcriptional factor, wherein the inhibitory agent binds with sufficient binding affinity to modulate transcription of a gene. The transcriptional factor has a DNA-binding domain distinct from an activation domain. Said modulation comprises dissociation of the transcriptional factor from the DNA of said gene and inhibits binding of the transcriptional factor to the DNA of the gene. The transcriptional factor is involved in a specific disease process, which is sarcoma. The transcriptional factor comprises an oncogenic fusion protein with a DNA-binding function. The fusion protein is tumor specific, or specific for sarcoma. The fusion protein is encoded by a chromosomal translocation comprising two or more genes or portions of genes. Said gene or portion of gene is a b-ZIP transcription factor ATF1 and said fusion protein is EWS/ATF1. The inhibitory agent is an antibody or a subcomponent of an antibody, or a monoclonal antibody.

Claims 1-4, 8-14, 17-20 encompass an *"in vivo"* method for modulating transcriptional factor-mediated gene expression.

The disclosure of the specification has been set forth above.

Briefly, the specification discloses that antibody mAb4 inhibits transcription using a murine proliferating cell nuclear antigen gene promoter (PCNA) as template (p.52), and that expression of sFc4 in Hela cells transfected with pEWS/ATF1 decreases the reporter CRE-luc expression, suggesting that sFv4 is capable of inhibiting CRE activation by EWS/ATF1 in Hela cells, and consequently inhibiting transcription of genes (Example 17 on pages 85-86). The specification also discloses that expression of sFv4 in tumor cell line SU-CCS-1 endogenously expressing EWS/ATF1 fusion protein decreases the expression of CRE-luc reporter, and leads to loss of viability and apoptosis (Examples 17-18, on pages 86-90). The specification discloses that tumorigenecity of the CCS cell line in nude mice has ben demonstrated, and is highly reminiscent of Clear Cell Sarcoma tumor in human. The specification contemplates the use of sFv for inhibiting tumorigenecity of cells in nude mice (p.81, second paragraph).

One cannot extrapolate the teaching in the specification to the claims, because the enablement of the claimed invention appears to be based solely on in vitro data. The art however does not recognize a reliable correlation between in vitro assay data and effective in vivo efficacy for human tumor immunotherapy using antibodies. This is evidenced Kimmel et al.(J. Neurosurg, 66:161-171, 1987) who teach that in vitro assays cannot easily assess host-tumor and cell-cell interactions that may be important in the malignant state and cannot duplicate the complex conditions of in vivo therapy.

Further, it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in cell-cell interactions, and homeostasis. Hummler E et al, 1994, PNAS, USA, 91: 5647-5661 teach that there is compensation within the CREB/ATF family of transcription factors, wherein mice with disruption of the CREB gene appear to be healthy, and has an increase level of CREM, another member of the CREB/ATF family, and no change in the level of ATF1. Hummler E et al conclude that CREB is not the sole mediator of camp-dependent transcriptional regulation, and probably acts in concert with a specific subset of cAMP responsive element-binding proteins to transduce the cAMP signal and in its absence, these same proteins can compensate for CREB function. Gottschalk, AR, 1996, Cell Death Differ., 3(1): 113-118 teach that regulation of a cell's apoptotic threshold is likely to result from a complex set of interactions among Bcl-2 family members and other, as yet uncharacterized, regulators of apoptosis. Thus it is unpredictable that the antibody fragment sFv4, could be effective in inducing apoptosis in tumor cells in vivo, due to possible homeostasis regulation.

Further, characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer

cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather

skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on the cell culture data presented in the specification, it could not be predicted that, in the *in vivo* environment, bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus, based on the cell culture data presented in the specification, it could not be predicted that, in the *in vivo* environment, sFv4 would be effective in inhibiting gene expression, resulting in killing tumor cells.

Further, an anti-tumor agent must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of

time. In addition the target cell must not have an alternate means of survival despite action at the proper site for the drug. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the anti-tumor agent is in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure to the target site may be delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieveing successful therapy. The sFv peptide may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the protein and the *in vitro* tests of record do not sufficiently duplicate the conditions which occur *in vivo*. In addition, the sFv peptide may not otherwise reach the targert because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the sFv peptide has no effect, circulation into the target area may be insufficient to carry the peptide and a large enough local concentration may not be established.

Moreover, one cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in

the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed method would be effective in inhibiting gene expression in vivo resulting in apoptosis of tumor cells. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed method would be effective in inhibiting gene expression in vivo resulting in apoptosis of tumor cells. . In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are

unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

In view of the above it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102(a)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-4, 8-14, 17-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Bosilevac, JM et al, 1999, JBC, 274(49): 34811-8.

Claims 1-4, 8-14, 17-20 are drawn to a method for modulating transcriptional factor-mediated gene expression, comprising exposing said transcriptional factor to an inhibitory agent which binds to "a linker domain of said transcriptional factor", wherein said linker domain is located adjacent to the DNA binding domain of the transcriptional factor, wherein the inhibitory agent binds with sufficient binding affinity to modulate

transcription of a gene. The transcriptional factor has a DNA-binding domain distinct from an activation domain. Said modulation comprises dissociation of the transcriptional factor from the DNA of said gene and inhibits binding of the transcriptional factor to the DNA of the gene. The transcriptional factor is involved in a specific disease process, which is sarcoma. The transcriptional factor comprises an oncogenic fusion protein with a DNA-binding function. The fusion protein is tumor specific, or specific for sarcoma. The fusion protein is encoded by a chromosomal translocation comprising two or more genes or portions of genes. Said gene or portion of gene is a b-ZIP transcription factor ATF1 and said fusion protein is EWS/ATF1. The inhibitory agent is an antibody or a subcomponent of an antibody, or a monoclonal antibody.

Bosilevac, JM et al teach that transfection of scFv4, a single chain antibody derived from the anti-ATF1 monoclonal antibody mAb41.4, into a cell line derived from Clear Cell Saracoma results in a 90% reduction in cyclic AMP-response element-driven reporter activity, reduces viability and induces apoptosis of said cell line. Bosilevac, JM et al teach that sFv4 binds ot the first 15 residues N-terminal to the DNA binding domain of ATF1 (p. 34812, second paragraph). Bosilevac, JM et al teach that the antibody recognizes the EWS/ATF1 fusion protein, which is overexpressed in said cell line, and inhibits its binding to the CRE domain of target DNA (p.34813, last paragraph, bridging p.34814). Bosilevac, JM et al teach that the chimeric protein EWS/ATF1 is a result of translocation associated with Clear Cell Sarcoma, that fuses the genes for Ewing's sarcoma protein (EWS) to the activating transcriptional factor (ATF1) (abstract).

Bosilevac, JM et al do not teach that the transcriptional factor has a DNA-binding domain distinct from an activation domain, and that the method would result in dissociation of the transcriptional factor from the DNA of a gene.

The reference does not specifically teach that the transcriptional factor has a DNA-binding domain distinct from an activation domain. However, the targeted transcriptional factor in the claimed method appears to be the same as the prior art transcriptional factor. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Further, because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

REJECTION UNDER 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 8-14, 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Orten et al, 1994, JBC, 269(51): 32254-33263, or Bosilevac, JM et al, supra, in view of Brown et al, 1995, Oncogene, 10: 1749-1756.

Claims 1-4, 8-14, 17-20 are drawn to a method for modulating transcriptional factor-mediated gene expression, comprising exposing said transcriptional factor to an inhibitory agent which binds to "a linker domain of said transcriptional factor", wherein said linker domain is located adjacent to the DNA binding domain of the transcriptional factor, wherein the inhibitory agent binds with sufficient binding affinity to modulate transcription of a gene. The transcriptional factor has a DNA-binding domain distinct from an activation domain. Said modulation comprises dissociation of the transcriptional factor from the DNA of said gene and inhibits binding of the transcriptional factor to the DNA of the gene. The transcriptional factor is involved in a specific disease process, which is sarcoma. The transcriptional factor comprises an oncogenic fusion protein with a DNA-binding function. The fusion protein is tumor specific, or specific for sarcoma. The fusion protein is encoded by a chromosomal translocation comprising two or more genes or portions of genes. Said gene or portion of gene is a b-ZIP transcription factor ATF1 and said fusion protein is EWS/ATF1. The inhibitory agent is an antibody or a subcomponent of an antibody, or a monoclonal antibody.

Orten et al teach that monoclonal antibody mAb4 that binds to peptide c or amino acids 205-219 of the transcription factor ATF1 inhibits in vitro transcription of the murine

PCNA gene-LUC (p. 32259), by preventing binding of ATF1 to DNA binding via the cAMP responsive element (CRE) on the DNA.

It is noted that peptide (c) or amino acids 205-219 of ATF1 taught by Orten et al is exactly the same as the linker domain comprising amino acids 205-219 of the ATF-1 protein of SEQ ID NO:1, as disclosed on page 12 of the specification of the instant application.

Orten et al do not teach that the transcriptional factor is involved in a specific disease process, which is sarcoma, and comprises an oncogenic fusion protein with a DNA-binding function. Orten et al do not teach that the fusion protein is tumor specific, or specific for sarcoma. Orten et al do not teach that the fusion protein is encoded by a chromosomal translocation comprising two or more genes or portions of genes, and that said fusion protein is EWS/ATF1. Orten et al do not teach the use of a subcomponent of an antibody.

The teaching of Bosilevac, JM et al has been set forth above.

Brown et al teach that translocations involving fusion of the N-terminal region of EWS to other transcriptional factors are significant in the genesis of distinct primitive sarcoma, such as fusion of EWS to ATF1 in malignant melanoma of soft part, wherein 325 amino acids of EWS replace the N-terminal 65 amino acids of ATF1 (p.1749, second column, second and third paragraphs and figure 1 on page 1750). Brown et al teach that EWS/ATF1 is predicted to bind to ATF1 binding sites on the promoters via the ATF1 bZIP domain (p.1749, second column, third paragraphs). Brown et al teach that EWS/ATF1 could act as activater of some ATF-dependent promoters and as

repressor of others in JEG3 cells and tumor cell line DTC1 and SU-CCS-1 expressing EWS/ATF1, wherein the transcriptional activation by EWS/ATF1 is dependent on the ATF-1 binding site of the promoters (p.1750).

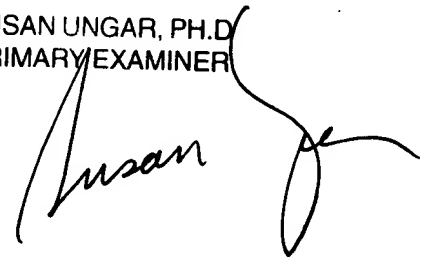
It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to use the method of Orten et al for modulating gene expression in a target cell expressing ATF-1 by exposing the transcriptional factor ATF-1 to the antibody mAb4 as taught Orten et al. It would have been obvious to replace cells expressing ATF-1 with cells expressing the fusion protein EWS/ATF1, and to modulate gene expression using mAb4 taught by Orten et al, because of the following reasons: 1) Similar to ATF-1, EWS/ATF1 could modulate gene expression via the ATF-1 binding site of the target promoters, as taught by Brown et al, 2) EWS/ATF1 has been shown to express in sarcomas, as taught by Brown et al, and 3) One would have expected that mAb4 taught by Orten et al by binding to ATF1 part of EWS/ATF1 via amino acids 205-219 of ATF1 could disrupt the binding of ATF1 to the promoter containing ATF-1 binding sites, similar to the action of mAb4 on ATF1 alone, because one would have expected that the region surrounding the DNA binding domain would be similar in both ATF-1 and EWS/ATF1, such that simlar to ATF1, EWS/ATF1 could bind to DNA and modulate transcription of genes . One of ordinary skill in the art would have been motivated to modulate transcription factor-mediated gene expression with a reasonable expectation of success. The motivation is obvious, i.e. modulate gene expression in cancer cells that express EWS/ATF1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER



MINH TAM DAVIS

August 21, 2003